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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,471	TAKANO ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *2-8,10,12,14,16-18 and 24-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,11,13,15 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Alignment*.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on October 3, 2003), Applicants filed an election and amendment received on November 17, 2003 and January 8, 2004, respectively. Said amendment amended Claims 19-28. Claims 1-32 are pending in the instant Office action.

Election

2. Applicant's election without traverse of Group I, Claims 1, 9, 11, 13, 15, and 19-23, in a paper received on November 17, 2003 is acknowledged. Claims 1-32 are pending in the instant Office action. Claims 2-8, 10, 12, 14, 16-18, and 24-32 are withdrawn from consideration as non-elected inventions. Claims 1, 9, 11, 13, 15, and 19-23 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/242,561 filed on October 23, 2000 as requested in the declaration and the first lines of the specification.

Information Disclosure Statement

4. The information disclosure statement filed on February 2, 2004 fails to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion

which caused it to be listed. The following references were not considered for the reasons described below:

a) Chater *et al*. has no date in the citation.

b) EMBL AJ007731 is an incomplete citation.

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto. The Examiner notes the correction of a typographical error in the author's name of reference C23; no action is required by Applicants.

Objections to the Specification

5. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Methods of Increasing Antibiotic Production in *Streptomyces* by Deletion of the *scbA* Gene---

6. The specification is objected to for inappropriate notation of an internet address. On page thirteen, line 9, an internet address is cited in an unacceptable form. See M.P.E.P. § 707.05(e) for the acceptable notation of an internet address.

7. The specification is objected to for a typographical error on page 32, line 3, wherein the author "Onishi" is misspelled; the correct spelling is ---Ohnishi--- as found throughout the specification, for example on page 32, line 32. Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 9, 11, 13, 15, and 19-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The nature and/or structure of the *scbA* gene for deletion are unclear in *S. lividans*. The specification describes the *scbA* gene of *S. coelicolor*. While the specification teaches deletion in *S. lividans* using an *scbA* deletion mutant allele from *S. coelicolor* (see page 29), no identification of an *scbA* gene in *S. lividans* is described. In view of the homologue names of barX (*S. virginiae*) and afsA (*S. griseus*), the nature and/or structure of the gene to be deleted in *S. lividans* are unclear without specific identification either in the specification or the art of an *scbA* gene per se. Clarification is required.

9. Claims 15 and 19-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "homologue" is unclear as to its exact nature. On page 11, a homologue is described as the gene with the highest sequence identity to scbA; this definition is wholly unfounded considering that not all *Streptomyces* strains have identified an scbA gene or even the functionality of said gene. Moreover, no description of a functional relationship between scbA and its homologues is noted in the specification or the claims; is one required, which is typical of homologues in the art? Clarification on these points is required.

10. Claims 19-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 19, items (a) and (b) are confusing since the portion of EMBL AJ007731 is identical to the portion of SEQ ID NO:19.

Also in item (a), inclusion of an accession number lacks clarity because the sequences in such accession numbers can be altered. Thus, the exact nature of AJ007731 is unclear.

In Claim 19, item (d), the phrase "the amplify total DNA of said species or strain" is wholly unclear as to its intent in view of the oligo primers in the item; it would seem that amplification of scbA is more appropriate. Clarification on all these points is required.

11. Claims 19-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "about" with respect to % identity is unclear in the instant claims. The specification teaches no concept of how much variation the term "about" can garner into the scope of the claims. The art is wholly inconsistent on this point – does "about" mean $\pm 1\%$, $\pm 5\%$, $\pm 10\%$? Clarification is required.

12. Claims 20-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "the level of sequence identity" is unclear as a further limiting feature of Claims 20-23. Is this limitation meant to limit only item (c)? How about item (d)? The scope of Claims 20-23 is, thus, wholly unclear. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 9, 11, 13, 15, and 19-23 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for deleting the scbA gene, does not reasonably provide enablement for function deletion of the scbA gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To make all the strains having functional deletions of the scbA gene intended in the claims, in view of the specification, would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the specification on page 9, functional deletion is described to include any alteration, which effects normal expression of that gene. Within this definition is included the alteration of "the transcriptional and/or translational regulatory sites ... to prevent normal transcription and/or translation of the gene." No such examples of functional deletion are described in the specification. No direction for the identification of regulatory regions of scbA and its homologues is described. The nature of the invention is that regulation of genes can be very complex, particularly in the production of antibiotics in bacteria, and without direct teachings of regulation of scbA or its homologues, the ability to predict both regulatory sequences within the genes as well as their regulatory effects is very low. Thus, Claims 1, 9, 11, 13, and 15-23 are not enabled to the full extent of their scope.

14. Claims 15 and 19-23 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for deleting *scbA* homologs in *Streptomyces* with a known homolog to test for antibiotic production, does not reasonably provide enablement for deleting *scbA* gene homologs in *Streptomyces* without a known homolog. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To test all *Streptomyces* strains having deletions of *scbA* gene homologs would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above. The claims provide no clear limitations on the nature of the *scbA* gene (or its homologs) to be deleted; the structure is extremely vague and unclear and no function is described in the specification of the claims. Thus, one of skill in the art must delete genes virtually at random to affect antibiotic production. Such methods would require copious experimentation that is wholly unpredictable since it is clear from the art that *scbA* homologs, such as *afsA* and *barX*, are inconsistent in their effects on antibiotic production (see Horinouchi *et al.* and Kawachi *et al.* in the art rejections below). Thus, the claims are not enabled to the full extent of their scope.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 15 and 19-23 are rejected under 35 U.S.C. § 102(b) as being anticipated by Horinouchi *et al.* (1989, see IDS). The instant claims are drawn to methods of identifying *Streptomyces* by deleting *scbA* gene homologs and assaying for antibiotic production.

Horinouchi *et al.* teach the deletion of afsA, an scbA homolog as noted in the specification, using various plasmids and assaying for streptomycin production (see page 1207 and Table 1). While the structural limitations are not clear in the claims, the Examiner notes that

the *S. griseus* gene taught by the art encodes a protein that is 64% identical to SEQ ID NO:17 (see attached alignment).

16. Claims 15 and 19-23 are rejected under 35 U.S.C. § 102(a) as being anticipated by Kawachi *et al*. (Identification of an AfsA homologue (BarX) from *Streptomyces virginiae* as a pleiotropic regulator controlling autoregulator biosynthesis, virginiamycin biosynthesis and virginiamycin M_1 resistance. Molecular Microbiology (April, 2000) 36(2):302-313). The instant claims are drawn to methods of identifying *Streptomyces* by deleting *scbA* gene homologs and assaying for antibiotic production.

Kawachi *et al*. teach the deletion of barX, an scbA homolog as noted in the specification, and assaying for antibiotic production (see Abstract and page 305). While the structural limitations are not clear in the claims, the Examiner notes that the *S. virginiae* gene taught by the art encodes a protein that is 34% identical to SEQ ID NO:17 (see attached alignment).

Other Notable Art

17. The following are cited to complete the record; these references are not prior art:

a) Takano *et al*. A complex role for the gamma-butyrolactone SCB1 in regulating antibiotic production in *Streptomyces coelicolor* A3(2). Molecular Microbiology (2001) 41(5):1015-1028.

b) Butler *et al*. Deletion of scbA enhances antibiotic production in *Streptomyces lividans*. Appl. Microbiol. Biotechnol. (2003) 61:512-516.

c) GenBank Accession Number NP_823445. putative gamma-butyrolactone biosynthesis protein [*Streptomyces avermitilis* MA-4680] (2004).

Conclusion

18. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Examiner
Art Unit 1652

March 17, 2004